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| 09/306,006 | 05/06/1999 | ANDREAS WERNER SUPERSAXO | NB/2-21551/A | 2914 |

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| EXAMINER |
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SHARAREH, SHAHNAM J

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| ART UNIT | PAPER NUMBER |
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1617

DATE MAILED: 05/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/306,006

Applicant(s)

SUPERSAXO ET AL.

Examiner

Shahnam Sharareh

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 January 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2, 6, 16, 17, 19-21, 28 and 30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2, 6, 16, 17, 19-21, 28 and 30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 3/18/05, 1/27/05
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 27, 2005 has been entered.
2. The Amendment filed on January 27, 2005 has been entered. Claims 2, 6, 16-17, 19-21, 28, 30 are now pending and under consideration.
3. Applicant's arguments with respect to the pending claim have been considered but are moot in view of the new ground(s) of rejection. The new ground of rejection employs an additional prior art to further clarify the state of art about the use of polyoxyethylene type surfactants in pharmaceutical dispersions.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

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2. Ascertaining the differences between the prior art and the claims at issue.
 3. Resolving the level of ordinary skill in the pertinent art.
 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
4. Claims 2, 6, 16-17, 19-21, 28, 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yiv et al US Patent 6,245,349 in view of Weder WO 96/37192 (WO '192) and EP 0349 160 A2 (EP '150).
5. The instant claims are directed to methods of preparing aqueous monodisperse nanodispersion formulations having Gaussian distribution, which steps consisting forming a mixture (α) by mixing components consisting essentially of (a) 0.1-30% by weight of phospholipids, (b) 1-50% by weight of polyoxyethylene type coemulsifiers such as polyethoxylated fatty acids, polyethoxylated carbohydrates and polyfethoxylated fatty alcohols, (c) 0.1-80% by weight of a lipophilic component which comprise a natural or synthetic or a partial synthetic c4-c 18 triglyceride and a lipophilic active agent, (and d) 0.63-1,42% by weight ethanol, wherein the sum of (a) (b) (c) and (d) is 100 percent and then mixing the mixture (α) with a water phase.

Applicant attention is drawn to the lipophilic component of mixture (α). Said component uses the transitional phrase "comprises." Accordingly, Examiner construes any lipophilic entity in combination with a natural or synthetic triglyceride and a lipophilic pharmaceutical active agent to meet this limitation. Such lipophilic entity can include cholesterol, ceramides, etc..

6. Yiv et al disclose methods of preparing delivery compositions comprising particles having a size below about 50 nm diameters. (col 5, lines 1-10). The compositions of Yiv comprise a lipophilic drug such as antifungal azoles, a

phospholipids (Centrophase 31), a nonionic polyoxyethylene coemulsifier (Tween 80 which is polyoxyethylene 20 sorbitan monooleate and viewed to fall within scope of the instant polyethoxylated carbohydrates) and a lipophilic component, which is a triglyceride or propylene glycol diester oil having C6 to C 14 carbons for the total of 100% weight. (col 5, line 50-col 6, line 65; col 17, lines 5-25; col 9, lines 14-60; col 11, line 1-29). Yiv clearly set's forth other functional equivalents that can be used as his polyoxyethylene coemulsifier component. For example, at col 6, lines 6-36, Yiv describes the proper criteria for suitable coemulsifiers. Specifically Yive provides for their HLB values and recites numerous surfactants within the scope of the instant claims. i.e. polyoxyethylene stearates, polaxomers.. Finally, the concentrations of each of Yiv's components fall within the instantly claimed ranges (see tables 1.3, 3.1, 5.1; claims 1-8).

Yiv's methods do not employ high shear mixing equipments. In fact they employ an apparatus comprising a stirring magnetic bar which is the same mechanism instantly disclosed (see col 8, lines 18-25; col 11, lines 20-26). Yiv teaches that lower alcohols such as ethanol may be used in his composition in place of the polyethylene glycol if so desired. (see col 7, lines 10-15). Yiv fails to specifically use ethanol in his formulation.

7. The WO '192 and EP '150 are merely used to show that the use of ethanol as the carrier system in an emulsion type delivery system and nonionic surfactants such as polyoxyethyelene coemulsifiers are well established in the art.

8. WO'192 patent teaches the use of ethanol in nanodispersion compositions. The methods of preparing nanodispersion described in WO '192 are similar to those described in Yiv comprising similar components as in Yiv. The nanodispersions

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prepared in WO '192 are compositions comprising phospholipids, polyoxyethylene surfactants, lipophilic component including triglycerides, cholesterol and therapeutic agents in combination with ethanol. (see the entire pages 9-15 under components (a)-(g), especially page 12, lines 1-20; page 1; [age 22, example 1-page 25, example 4).

The sizes of the colloidal particles are typically between 30-50nm which meets the limitations of the instant claims. (page 20, line 16-22). WO '192 teaches that it is well within purview of an ordinary skill in the art to select a suitable carrier system for the intended pharmaceutical or cosmetic use. Accordingly, using ethanol to form an aqueous dispersion is conventional depending on the utility of the formulation. WO '192 also encourages the use of triglycerides in nanodispersion composition to improve stability of the composition.

9. EP '150 is used to show that in the art of preparing aqueous pharmaceutical dispersions, nonionic surfactants are essentially art recognized functional equivalents. Such surfactants include polyoxyethylene sorbitane fatty esters, polyoxyethylene alkyl ethers, polyoxyethylene phytosterol, polyoxyethylene lanolin derivatives, polyoxyethylene alkyl amines etc.. (see page 3, lines 25-35). EP '150 only differs from the instant claims as it employs high shear mixing mechanism.

Thus, even though Yiv fails to use ethanol in his composition it would have been obvious to one of ordinary skill in the art at the time of invention to add ethanol into Yiv's carrier system as suggested by Yiv's patent itself and exemplified in WO '192, because the ordinary skill in the art would have had a reasonable expectation of success to

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enhance the delivery of Yiv's active agent to any specific tissue when adding adequate amount of ethanol.

Further, absent a showing of unexpected results it would have been obvious to use any nonionic polyethoxylated surfactant system, as enumerated in EP '150, in Yiv's composition in combination or in place of Tween 80, because as described in EP '150, they are art recognized functional equivalents and one of ordinary skill in the art would have had a reasonable expectation of success in using similar properties when used to form a colloidal dispersion.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 2, 6, 16-17, 19-21, 28, 30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 32-37 of copending Application No. 10/016,903. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claims are directed to same process steps, except that the copending application uses a higher

minimum concentration of ethanol in the formulation. Nevertheless, once in possession of the copending claims, it would have been obvious to one of ordinary skill in the art at the time of invention to practice the scope of the instantly pending claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

11. Even though Examiner has applied a new ground of rejection using an additional prior art to better define the reasons of prior art rejection, Examiner would hereby respond to Applicant's arguments for the sake of clarifying the record with respect to the interpretation of the term Tween 80.

12. Applicant argues that neither of the cited references teaches the use of the instantly claimed polyoxyethylene co-emulsifiers enumerated in element (b) of the instant claims. Relying on the CTFA database and page 1059 of the textbook Wade, Organic Chemistry, and Applicant argues that Sorbitan derivatives is not within the scope of the instantly claimed polyethoxylated carbohydrates. (see Remarks at page 4-5). Applicant appears to argue that Tween 80 is a polyethoxylated sorbitan fatty ester which is excluded from the instant claims 28 because it is not a polyethoxylated carbohydrate, rather a fatty acid derivative thereof.

13. In response Examiner states that during patent examination the scope of the claims are given their broadest reasonable interpretation consistent with the teaching of the Specification,. See MPEP 2111. Here, the term polyethoxylated carbohydrate is not defined in the specification. Accordingly, Examiner has interpreted the term Tween 80

given the broadest reasonable interpretation consistent with the state of art Attention is drawn to attached chemical definition and structure of polyoxyethylene sorbitan oleate 20 or Tween 80.

(www.chemicaland21.com/arokorhi/specialychem/perchem/polyoxyethylene%20SOR, 3/3, last visited 5/10/05). This is the same surfactant that is used in the primary and the secondary references.

As shown by the structure and further described in line 1-7 of the general description, Sorbitol is a sugar alcohol and sorbitan is the anhydride form of sorbitol and thus is a carbohydrate. Since the specification does not exclude such moiety from the limitation "polyoxyethylated carbohydrates," Tween 80 falls within the scope of such claims. In fact, the polyethoxylated moieties at the hydroxyl positions of sorbitan molecule end with a hydroxyl group and fall within the scope of the instantly claimed polyethoxylated fatty alcohols. Thus, contrary to applicant's arguments Tween 80 falls within the enumerated coemulsifiers of the instant claims.

Further, Applicant remarks seem to suggest that the instantly claimed polyethoxylated carbohydrates may include as hydrates not dehydrates. (see remarks at page 4 last two lines). In response, Examiner states that for purposes of applying a prior art rejection during the prosecution of a patent application, Examiner must view the limitations given their broadest reasonable interpretation, not a possible meaning that a limitation may have. In fact, Applicant attempt to narrow the claim limitation is improper and does not exclude the use of sorbitans.

Declaration filed under 37 CFR 1.132 By Dr. Supersaxo

14. The declaration under 37 CFR 1.132 filed on January 10, 2005 is insufficient to overcome the rejection of claim 2, 6, 15-21, 28-29 based upon the rejection as set forth in the last Office action.

The scope of the declaration is not commensurate with the scope of the claims, because it does not provide sufficient evidence of unexpected results. The declaration presented evaluates the nanoparticles of the prior art with those of the instant invention. The declaration then concludes that the particle size created by prior art using a polyhydric alcohol is larger than those created according to the invention using ethanol.

In response, Examiner states again that the nanoparticles of the prior art both in Yiv and Weder, still create a particle size and appearance characteristics that is within the scope of the instant claims. They both create an opalescent, transparent and homogenous formulation having particle size smaller than 50nm. Further, the instant claims such characteristics and particle size and does not exclude the particle sizes described in the prior art. In fact, the declaration reinforces the teachings of prior art. The fact that particle sizes of the instantly claimed methodology are smaller than 18 nm is not relevant because the scope of the instant claims is not directed to such particle sizes. Therefore, no evidence of unexpected results are presented.

Conclusion

15. **No claims are allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 571-272-0630. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER